Amendments to the Drawings:

The two attached sheets of drawings includes changes to Fig. 5. These two sheets, which include Fig. 5, replace the original sheet including Figures 5 and 6. In Figure 5, drawing element numbers have been added.

Attachment: Two Replacement Sheets
Annotated Sheet Showing Changes to Figure 5.

REMARKS/ARGUMENTS

In response to the pending Office Action of June 7, 2004, Applicants present the following arguments and amendments. The present amendments are requested to more clearly describe and claim the present invention and do not introduce any new matter. Applicants submit that in light of the arguments presented and amendments requested this application is in condition for allowance. Therefore, reconsideration and withdrawal of all pending rejections is respectfully requested.

A Petition for a One Month Extension of Time and the required fees are provided with this response. With the entry of this amendment, claims 1 - 71 are pending herein.

Amendments to the Specification

Amendment of the paragraph beginning on line 19, page 20 is requested to change the recitation "photograph" to recite "schematic diagram illustrating a top plane view." The requested amendment conforms the description of Figure 5 to the replacement Figure 5 provided with this response. The requested amendment improves clarity and does not introduce new matter.

Amendments of the paragraphs beginning on line 9, page 32 and the paragraph beginning on line 30, page 32 are respectfully requested to reference drawing elements numbers added to Figure 5. The requested amendments improve clarity and do not introduce new matter.

Amendments to the Drawings

Amendments to Figure 5 are requested to add drawing element numbers corresponding to the description of this figure in the specification and to convert

the Figure to a schematic diagram conforming to the drawing requirements of the U.S. Patent and Trademark Office. Support for the requested amendments is provided by the text box descriptions of drawing elements provided on Figure 5 as originally filed and the description of Figure 5 beginning on page 32, line 9 and ending on page 33, line 4. The requested amendments improve clarity and do not introduce new matter.

<u>Amendments to the Claims</u>

Amendments of claim 1, 39, 60 and 62 are requested to more particularly point out and distinctly claim the present invention. Amended claim 1 recites "wherein the distribution of transmitted wavelengths is continuously tunable by adjustment of the selectably adjustable wavelength selector." Amended claims 39, 60 and 62 provide the step of "tuning the center wavelength of said distribution of transmitted wavelengths by adjusting said selectably adjustable wavelength selector to transmit light having a continuously tunable distribution of wavelengths." Support for the requested amendments is provided by the description of an embodiment of the present invention have a wavelength selector "capable of selectively adjusting the center wavelength of a distribution of transmitted wavelengths over a continuum of values" on page 11, lines 28 – 30. In addition, support for the requested amendment is provided by the description beginning on page 12, line 12 and ending on page 14, line 7 of the operation and functional benefits of a surface plasmon resonance sensor of the present invention wherein "the center wavelength of the distribution of transmitted wavelengths may be continuously varied while SPR measurements or images are collected." (page 13, lines 16 – 17). For example, embodiments are set forth and described on page 13, lines 21 – 24 that "provide the ability to continuously tune the wavelength distribution of excitation light, detected light or both [f]or a substantial range of wavelength, preferably over a range of at least 60 nm and

more preferably over a range of several hundred nanometers". The requested amendments do not introduce any new matter.

Amendments of claims 39, 60 and 62 are also requested to change the recitation "detecting said light with said detector" to recite "detecting said light having said distribution of transmitted wavelengths with said detector" and to change the recitation "adjusting said selectably adjustable wavelength selector to transmit light having a distribution of wavelengths selected to generate surface plasmons on a surface of said conducting layer in contact with said dielectric sample layer" to recite "adjusting said selectably adjustable wavelength selector to transmit light having a distribution of wavelengths that generates surface plasmons on a surface of said conducting layer in contact with said dielectric sample layer." The requested amendments enhance clarity and are supported by the description of methods of the present invention for generating SPR images and sensing changes in the refractive index of a probe region provided on page 10, lines 22 – 33, page 15, lines 23 – 29 and page 28, lines 7 – 12. The requested amendments do not introduce any new matter.

Amendments of claims 31 and 32 are requested to change the recitation "said first refractive index layer" to recite "said dielectric layer" and to change the recitation "comprise" to recite "are components of." The requested amendments improve clarity and correct antecedent basis. Amended claims 31 and 32 are supported by the description of exemplary SPR configurations "comprising waveguides, [and] fiber optic devices" useable in the present invention on page 14, lines 20 – 22. In addition, support is provided by the definition of SPR optical assembly beginning on page 24, line 31 and ending on page 25, line 6 which "may comprise waveguides, fiber optic devices or diffraction gratings." The requested amendments do not introduce any new matter.

Amendments of claims 10 and 13 are requested to change the recitation "wherein rotation of said optical interference filter selectably adjusts the distribution of transmitted wavelengths" to recite "wherein rotation of said optical interference filter selectably adjusts the tilt angle and distribution of transmitted wavelengths of said optical interference filter." In addition, amendments of claims 46 - 49 are requested to change the recitation "wherein rotation of said optical interference filter selectably adjusts the distribution of wavelengths of light which are transmitted" to recite "wherein rotation of said optical interference filter selectably adjusts the tilt angle of said interference filter and the distribution of wavelengths of light which are transmitted by said interference filter." The requested amendments improve clarity and are supported by the description on page 29, lines 7 - 22 of exemplary angular orientations of an optical interference filter as illustrated in Figure 3. Support for this amendment is also provided by the description of Equation VI beginning on page 29, line 24 and ending on page 30, line 5, which provides a quantitative relationship between the center frequency of an optical interference filter comprising a Fabry-Perot etalon and the tilt angle of the optical interference filter. The requested amendments do not introduce any new matter.

Amendments to claims 16 and 17 are respectfully requested to insert "filter" after the recitation "optical interference." The requested amendments correct an obvious typographical error and improve antecedent basis. The requested amendments do not introduce any new matter.

Amendment to claim 36 is respectfully requested to change the recitation "second layer" to recite "dielectric sample layer." Support for amended claim 36 is provided on page 31, lines 4 – 5. The requested amendment corrects an obvious clerical error and improves antecedent basis. The requested amendment does not introduce any new matter.

New claims 65 – 71 are provided to more particularly point out and distinctly claim the present invention. Support for new claims 65 – 71 is provided by the description beginning on page 28, line 23 and ending on page 29, line 5 of methods for correcting measured percent reflectivities for polarization dependent transmission of light transmitted through optical interference filters used in SPR methods of the present invention. In addition, support is provided in the characterization of an exemplary SPR sensor in Example 1 on page 33, lines 6 – 31 and in the correction curve provided in Figure 6. New claims 65 – 71 do not introduce any new matter.

Objections to the Drawings

The Examiner has required a new corrected drawing asserting that "Fig. 5 is undecipherable." Applicants submit with this response an amended Figure 5 that provides a schematic of a top plan view of a SPR sensor of the present invention and that replaces the text original present in Fig. 5 with drawing element numbers. Applicants submit that as amended with this response Fig. 5 conforms to the drawing requirements of the U.S. Patent and Trademark Office. Accordingly, withdrawal of the pending objection to the drawings is respectfully requested.

The drawings have been objected to under 37 CFR 1.83(a). In support of this objection, the Examiner asserted that "the waveguide and optical fiber of claims 31 and 32 must be shown or the feature(s) cancelled from the claims(s)." As amended with this response, claims 31 and 32 are directed to embodiments wherein refractive index layer and conducting layer of a SPR optical assembly are elements of an optical fiber or waveguide, respectively. Applicant submit that Figures 1 and 2 clearly show all the elements of claims 31 and 32 and that the references to a optical fiber and a waveguide in these claims merely indicate the nature of refractive index layer and the conducting layer device elements recited in the claims (i.e. designates the refractive index layer and the conducting layer

as components of an optical fiber or waveguide) rather than indicating new device elements needed to be indicated in the drawings.

Rejections under 35 U.S.C. § 112

Claims 31 and 32 have been rejected under Section 112, second paragraph, for allegedly lacking antecedent basis for the recitation "said first refractive index layer." Applicants request amendment of claims 31 and 32 to change the recitation "first refractive index layer" to recite "said dielectric layer." Applicant submits that as amended claims 31 and 32 provide sufficient antecedent basis and, therefore, respectfully requests reconsideration and withdrawal of the pending rejections of these claims.

Claims 31 and 32 are also rejected under Section 112, second paragraph, as allegedly "being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention." Applicants respectfully traverse this rejection. Claims 31 and 32, as amended with this response, are directed at embodiments of the present invention wherein the refractive index layer and the conducting layer of the SPR optical assembly comprise elements of a wave guide or optical fiber, respectively. As understood in the art of optics, waveguides and optical fibers are devices that collect, focus and/or transmit light by providing a plurality of refractive index layers that generate total internal reflection of light impinging upon these devices at a range of incident angles (*See* Exhibit A, descriptions of the composition and operation of optical fibers and waveguides). As taught on page 2, lines 29 - 39, these device elements may be used in SPR sensing and imaging methods by incorporating a thin metal layer such that "surface plasmons are created by evanescent fields generated as light propagates down a fiber optic or waveguide having a thin metal interior layer." Applicants submit that in light of the teaching in the specification and general knowledge in the art of optics, amended claims 31 and 32 particularly point out and distinctly claim the present invention.

Therefore, reconsideration and withdrawal of the pending rejections is respectfully requested.

Claim 36 is rejected for lacking sufficient antecedent basis for the element "said second layer." With entry of this amendment, claim 36 is change to recited "said dielectric sample layer" rather than "said second layer." Applicant submits that as amended claim 36 provides sufficient antecedent basis and, therefore, respectfully requests reconsideration and withdrawal of the pending rejection.

Rejections under 35 U.S.C. § 102

Claims 1-8, 10, 11, 13, 14, 16, 17, 19-22 & 25 - 64 have been rejected under Section 102(b) as allegedly anticipated by International Publication No. WO 01/69209 (Johansen *et al.*). In support of this rejection, the Examiner characterizes Johansen *et al.* as disclosing:

> A surface plasmon resonance sensor for sensing the refractive index of a probe region (pg. 9, line 16 – pg. 10, line 18) comprising a polychromatic light source 800 for generating light propagating along an incident light propagation axis, a polarizer 870 in optical communication with said polychromatic light source 800 for selecting the polarization state of said light, an optical assembly 880, 883, 886 in optical communication with said polychromatic light source 800 . . . and a selectably adjustable wavelength selector 860 positioned in the optical path between said light source 800 and said detector 920 for transmitting light having a distribution of transmitted wavelengths selected to generate surface plasmons on a surface of said conducting layer (Fig. 2c, 220) in contact with said dielectric sample layer (pg. 6, line 28 – pg. 7, line 26 & pg. 10, line 20 – pg. 11, line 2).

Amendment of the rejected claims is requested to more clearly specify the claimed invention, and Applicants request reconsideration and withdrawal of the rejections in light of the following arguments.

First, amended claims 1-8, 10, 11, 13, 14, 16, 17, 19 - 22 & 25 – 64 are not anticipated by the cited reference because they provide surface plasmon resonance (SPR) sensors and SPR imaging and sensing methods that are functionally distinguishable from the device configurations disclosed in Johansen *et al.* As amended with this response, claims 1-8, 10, 11, 13, 14, 16, 17, 19 - 22 & 25 – 64 are directed to SPR sensors and SPR imaging and sensing methods employing a selectably adjustable wavelength selector for transmitting light having a **continuously tunable** distribution of wavelengths. Although Johansen *et al.* provide SPR devices that also employ an adjustable wavelength selector, the teaching in this reference does not disclose or enable use of adjustable wavelength selectors capable of transmitting light having a continuously, tunable distribution of wavelengths. Rather, the device configurations set forth this reference are limited to embodiments using a rotating filter wheel capable of positioning one of a plurality of different optical interference filters each having a fixed angular position into an optical beam which is capable of providing **discrete selection** of the distribution of wavelengths of transmitted light. In contrast to the methods and devices of the rejected claims, the light detected using this optical configuration is constrained to one of a plurality of fixed wavelength distributions corresponding to each filter in the filter wheel. (See, e.g. Johansen *et al.* Examples 1 & 2, pg. 10, lines 25 – 27 & pg., 11, lines 9-10).

Functional distinctions between continuously tunable SPR devices and methods provided in the present invention and discretely selectable SPR devices in Johansen *et al.* accentuate significant advantages provided by the methods and devices of the present invention over conventional SPR methods. As the SPR resonance condition depends strongly on the wavelength distribution of light used to excite surface plasmons, SPR devices and methods of the present invention having a continuously, tunable distribution of wavelengths allow SPR resonance conditions to be accurately measured, characterized and optimized to provide SPR measurements having enhanced sensitivity and resolution. (*See*

e.g., pg. 11, line 25 – pg. 12, line 2). Applicants demonstrate that the ability to tune or scan the wavelength distribution of detected light over a continuum of values in the present methods and devices "allows accurate quantification of physical and chemical characteristics of a probe region . . . provides for a wide dynamic range of SPR sensors of the present invention . . . [and] eliminates the need for angle modulation to detect changes in the SPR resonance condition or determine a resonant wavelength or distribution of resonant wavelengths." (*See*, pg. 27 – pg. 14, line 2). Moreover, continuous wavelength tunability provides an important means "to enhance SPR image quality (i.e. optimal refractive index contrast within different areas of the probe region)," as demonstrated by the series of SPR images provided in Figures 12A – E (See, pg. 11, line 28 – pg, 29, line 2 & pg. 36, lines 5 – 17).

To clarify this important distinction between devices and methods of the rejected claims and the device configurations in Johansen *et al.*, rejected device claims 1-8, 10, 11, 13, 14, 16, 17, 19 - 22 & 25 – 38 are amended to recite the feature "wherein the distribution of transmitted wavelengths is continuously tunable by adjustment of the selectably adjustable wavelength selector" and rejected method claims 39 – 64 are amended to recite the step of "tuning the center wavelength of said distribution of transmitted wavelengths by adjusting said selectably adjustable wavelength selector to transmit light having a continuously tunable distribution of wavelengths." Applicants submit that this additional claim language clearly distinguishes the continuously, tunable SPR methods and devices of the amended claims from devices merely providing a discretely selectable wavelength distribution. As Johansen *et al.* does not disclose, enable or suggest all the limitations of the rejected claims, particularly SPR sensors or methods providing a continuously tunable wavelength distribution, this reference does not anticipate rejected claims. Accordingly, reconsideration and withdrawal of the pending rejections is respectfully requested.

Second, claims 10 – 17 and 46 – 49 are not anticipated by the cited reference because they provide surface plasmon resonance (SPR) sensors and SPR imaging and sensing methods employing a wavelength selector having an optical geometry that is fundamentally different from the optical geometry of the wavelength selector disclosed in Johansen *et al.* In support of the pending rejections, the Examiner characterizes Johansen *et al.* as disclosing an optical interference filter that is:

> . . .rotationally adjustable about an axis which is orthogonal to said incident light propagation axis, wherein rotation of said optical interference filter selectably adjusts the distribution of transmitted wavelengths (Fig. 8b, pg. 9, lines 6 – 11).

Applicants respectfully disagree with this characterization. Johansen *et al.* does not disclose an optical geometry having an **<u>optical interference filter</u>** that is rotationally adjustable about an axis **<u>orthogonal</u>** to an incident light axis. Rather, the optical geometries disclosed in Johansen *et al.* are limited to a **<u>rotating filter wheel</u>** which rotates about a rotational axis **<u>parallel</u>** to the propagation axis of an incident light beam thereby periodically moving a plurality of orbiting interference filters into and out of the path of an incident light beam (see e.g., Johansen *et al.*, pg. 9, lines 6 – 11, pg. 10, lines 24 – 27, pg. 11, lines 7 – 12, & Figs. 8a, 8b, 9). As shown in Figures 8a and 8b of Johansen *et al.*, rotation of the filter wheel **600** maintains a fixed angular orientation of filters **610a**, **610b** and **610c** of normal incidence with respect to the propagation axis of an incident light beam, and the rotational position of filter wheel **600** determines which interference filter intersects the propagation axis of the incident beam **110**. In contrast, the devices and methods of the rejected claims employ an optical geometry wherein an optical interference filter is itself rotated about a rotational axis orthogonal to the incident light or reflect light propagation axes, thereby accessing a variety the angular orientations (i.e. tilt angles).

To clarify these important structural differences between the optical geometries of wavelength selectors used in the present methods and in Johansen et *al.*, device claims 10 and 13 are amended to recite "wherein rotation of said optical interference filter selectably adjusts the tilt angle. . . of said optical interference filter" and method claims 46 – 49 are amended to recite "wherein rotation of said optical interference filter selectably adjusts the tilt angle of said interference filter." Applicants submit that this additional claim language clearly distinguishes the rotating interference filter of the amended claims having an interference filter with a selectively variable tilt angle from the rotating filter wheel of Johansen *et al.* providing a plurality of optical interference filters having a fixed angular orientation. As Johansen *et al.* does not disclose, enable or suggest all the limitations of the rejected claims, particularly use of an optical interference filter rotationally adjustable about an axis orthogonal to the incident light or reflected light propagation axis, this reference does not anticipate the rejected claims. Accordingly, reconsideration and withdrawal of the pending rejections is respectfully requested.

Third, claims 21, 22, 31 and 32 are not anticipated by the cited reference because Johansen *et al.* does not disclose each and every limitation of these reject claims. Contrary to the Examiner's characterization Johansen does not disclose or suggest a device configuration having a wavelength selector that is either a monochrometer or a spectrometer. Rather, the teaching in Johansen *et al.* is limited to wavelength selectors comprising rotating filter wheels having a plurality of optical interference filters. In addition, Johansen *et al.* does not disclose embodiments wherein the refractive index layer of an SPR optical assembly is either a waveguide or an optic fiber. Contrary to the Examiner's characterization, drawing element **300** in Figure 2D merely comprises a substrate supporting a metal layer **220**. Further, page 5, lines 30-31 and page 6, lines 15-16 of Johansen *et al.* do not describe use of an optical fiber as a component of an SPR optical assembly. Rather, these passages teach the generic use of an

optic fiber for coupling an optical beam to an SPR optical assembly or to a detector. Therefore, Applicants request reconsideration and withdrawal of the pending rejections, as Johansen *et al.* does not teach all the limitations in rejected claims 21, 22, 31 and 32.

Rejections under 35 U.S.C. § 103

Claims 12, 15, 18, 23 & 24 have been rejected under Section 103(a) as allegedly unpatentable over Johansen *et al.* in view of U.S. Patent No. 5,339,155 (Partridge *et al*). With respect to pending rejections of claims 12, 15 and 18, the Examiner asserts:

> Johansen substantially teaches the claimed invention except it fails to show an interference filter with an adjustable tilt angle range. Partridge shows that it is known to provide an interference filter with an adjustable tilt angle (col. 3, lines 23 – 28, Fig. 1, ref 10) for a spectroscopic measurement apparatus. It would have been obvious to someone of ordinary skill in the art to combine the device of Johansen with the interference filter having an adjustable tilt angle of Partridge for the purposes of providing selective wavelength transmission of the optical measurement beam (col. , lines 23 – 28).

With respect to pending rejections of claims 23 and 24, the Examiner asserts:

> Johansen substantially teaches the claimed invention except that it fails to show an interference filter comprising a prism or grating. Partridge shows that it is known to provide an interference filter comprising a prism or a grating (col. 5, lines 13 – 19, Fig. 2, ref. 10) for an optical wavelength modulating apparatus. It would have been obvious to someone of ordinary skill in the art to combine the device of Johansen with the interference filter having an adjustable tilt angle of Partridge for the purpose of providing selective wavelength transmission of the optical measurement beam (col. 5, 20 – 23).

Applicants respectfully traverse these rejections. Amendment of the rejected claims is requested, however, to more clearly specify the claimed invention.

Accordingly, Applicants request reconsideration and withdrawal of the rejections in light of the following arguments.

The arguments presented above relating to deficiencies of Johansen *et al.* are reasserted. Contrary to the Examiner's characterization, Applicants submit that Johansen *et al.* does not disclose, enable or suggest all the limitations of the rejected claims "except for the equation given by Applicant to define the center wavelength of a particular distribution of a band of wavelengths . . . an interference filter with an adjustable tilt angle range . . . [and] a prism or grating". First, the disclosure in Johansen *et al.* is limited to SPR sensors providing discrete wavelength selectablity, in contrast to the continuously tunable wavelength distribution provided by the devices of the rejected claims. Second, Johansen *et al.* does not disclose an optical geometry having an optical interference filter that is rotationally adjustable about an axis orthogonal to an incident light propagation axis. Rather, the optical geometry in Johansen *et al.* is limited to a rotating filter wheel which rotates about a rotational axis parallel to the propagation axis of an incident light beam. It is therefore submitted that no *prima facie* case of nonobviousness has been made out with respect to this rejection, and withdrawal thereof is respectfully requested.

In addition, claims 12, 15, 18, 23 & 24 are not rendered obvious by Johansen *et al.* in light of Partridge *et al.* because there is no express or implicit motivation or even suggestion in the references to combine their teachings to arrive at the inventions as claimed. Partridge *et al.* teach use of a rotating interference filter for wavelength selection in the context of long path optical absorption measurements which are **polarization independent** optical methods. In contrast, Johansen *et al.* teach use of a rotating filter holder in the context of SPR methods which are **highly polarization dependent** methods. Applicants submit that a person of ordinary skill in the art at the time of the invention would not be motivated to incorporate the interference filter optical geometry presented

in the context of Partridge *et al.*'s polarization independent optical absorption devices into Johansen *et al.* polarization dependent SPR devices. Moreover, in contrast to methods as taught in Partridge *et al.* providing an optical interference filter having a widely varying angular orientation, Johansen *et al.* teaches use of a rotating filter wheel that is specifically configured to provide discrete wavelength selectability while maintaining the interference filters in the filter wheel at a fixed angular orientation equal to normal incidence with respect to the propagation axis of an incident beam. (*See*, e.g., Johansen *et al.* Figs 8a, 8b, 9 and 10). Applicants submit that Johansen *et al.* actually teaches away from wavelength selection methods employing an optical interference filter having a variable angular orientation. In view of the divergent nature of the teachings in these references, a person having ordinary skill in the art would not be motivated to substitute the rotating interference filter disclosed in Partridge *et al.* for the rotating filter wheel in Johansen *et al.* It is therefore submitted that no *prima facie* case of nonobviousness has been made out with respect to this rejection, and withdrawal thereof is respectfully requested.

In addition, claims 12, 15, 18, 23 & 24 are not rendered obvious by Johansen *et al.* in light of Partridge *et al.* because a person of ordinary skill in the art at the time the invention was made would not have a reasonable expectation of successfully combining the teachings of these references to arrive at the inventions as claimed. Partridge *et al.* teach use of a rotating interference filter wavelength selector in the context of long path optical absorption measurements. While the absorption measurements of Partridge *et al.* are expected to be insensitive to the polarization states of the incident beam transmitted by the interference filter, SPR techniques are polarization dependent techniques because only incident light having a p-polarization state is capable of generating surface plasmons on the surface of the conducting layer. As shown in Figure 6 of the present application, optical interference filters, such as those described in Partridge *et al.*, exhibit polarization dependent transmission characteristics when

operated at tilt angles deviating from normal incidence. At wide tilt angles, such as such as "a 60° rotation of the filter from normal incidence" as taught by Partridge *et al.* (col. 5, lines 26 – 28), polarization dependent transmission of light passing through an optical interference filter becomes significant and can degrade a SPR measurement unless the measurement is corrected for differences in the p-polarized and s-polarized light intensities transmitted by the filter. (For a detailed description of this polarization dependent transmission effects in SPR imaging, see the description provided on pg. 33, lines 6 – 31, pg. 28, lines 23 – 33 & pg. 29, lines 1 - 5). A person of ordinary skill in the art at the time the invention was made would reasonably expect that integration of the rotating interference filter described in the context of the polarization-insensitive optical absorption methods of Partridge *et al.* into the polarization-dependent SPR methods in Johansen *et al.* would likely raise significant new experimental challenges involving the polarization dependent transmission characteristics observed for interference filters positioned at tilt angles deviating from normal incidence. Applicants submit, therefore, that a skilled artisan would not have a reasonable expectation of successfully combining the teaching regarding wavelength modulation in Partridge in the context of polarization sensitive SPR methods and devices. References which do not provide a reasonable expectation of successfully practicing the invention as claimed are not properly cited as prior art. *See, e.g.*, Amgen, Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 18 USPQ2d 1016, 1022 – 23 (Fed. Cir.), *cert denied*, 502 U.S. 856 (1991). It is therefore submitted that no *prima facie* case of nonobviousness has been made out with respect to this rejection, and withdrawal thereof is respectfully requested.

Claim 9 has been rejected under Section 103(a) as allegedly unpatentable over Johansen *et al.* With respect to this pending rejection, the Examiner asserts:

> even though the reference of Johansen does not specifically disclose the use of a linear interference filter, it does outline the importance of using an interference filter to filter out bands of selected wavelengths (pg. 9, lines 6-11). In light of the applicants disclosure, there is no critically distinguishing linear interference filter feature in the applicants disclosure that exemplifies novelty over prior art disclosure.

Applicants respectfully traverse this rejection. Amendment of claim 1, the claim that claim 9 depends from, is requested, however, to more clearly specify the claimed invention. Therefore, Applicants request reconsideration and withdrawal in light of the following arguments.

The arguments presented above relating to deficiencies of Johansen *et al.* are reasserted. Applicants submit that Johansen *et al.* does not disclose, enable or suggest all the limitations of the rejected claim, particularly SPR sensors providing a continuously tunable wavelength distribution. It is therefore submitted that no *prima facie* case of nonobviousness has been made out with respect to this rejection, and withdrawal thereof is respectfully requested.

Patentability of new claims

With entry of the present amendment, new claims 65 – 71 are added which are directed to methods for sensing the refractive index of a probe region and methods for generating an image of a probe region wherein correction is made for polarization dependent transmission of light transmitted through an optical interference filter used to filter an incident or reflected light beam. Applicants submit that the new claims are both novel and nonobvious because nowhere in the prior art are methods disclosed comprising the steps of: (1) determining correction factors by measuring the ratio of the intensity of p-polarized light transmitted by the optical interference filter to s-polarized light transmitted by the optical interference filter, and (2) calculating percent reflectivities corrected for polarization dependent transmission of light transmitted by the optical interference filter. Indeed, nowhere in the prior art is the

dependence of light transmitted by an interference filter on polarization state even identified. Further, Applicants reassert the arguments above relating to deficiencies in the teachings of Johansen *et al.* and Partridge *et al.* Accordingly, Applicants respectfully request allowance of new claims 65–70.

CONCLUSION

In view of the foregoing arguments, this case is considered to be in condition for allowance and passage to issuance is respectfully requested. If new issues of patentability are raised, the Examiner is invited to call and arrange for an opportunity to discuss these issues via phone interview.

It is believed that a one month extension of time is required with this submission. Therefore, a petition for a one month extension and fee of $ 55.00 are provided. In addition, extra claim fees of $151.00 are provided for the addition of 7 new claims including 2 independent claims. If this amount is incorrect, please charge the appropriate fees or credit any overpayment for this submission along with any extension of time required to Deposit Account No. 07-1969.

Respectfully submitted,

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APPENDIX

Application No. 10/696,738
Amendment dated 10/7/04
Reply to Office Action of June 7, 2004
Annotated Sheet Showing Changes

New Drawing Element Numbers Indicated

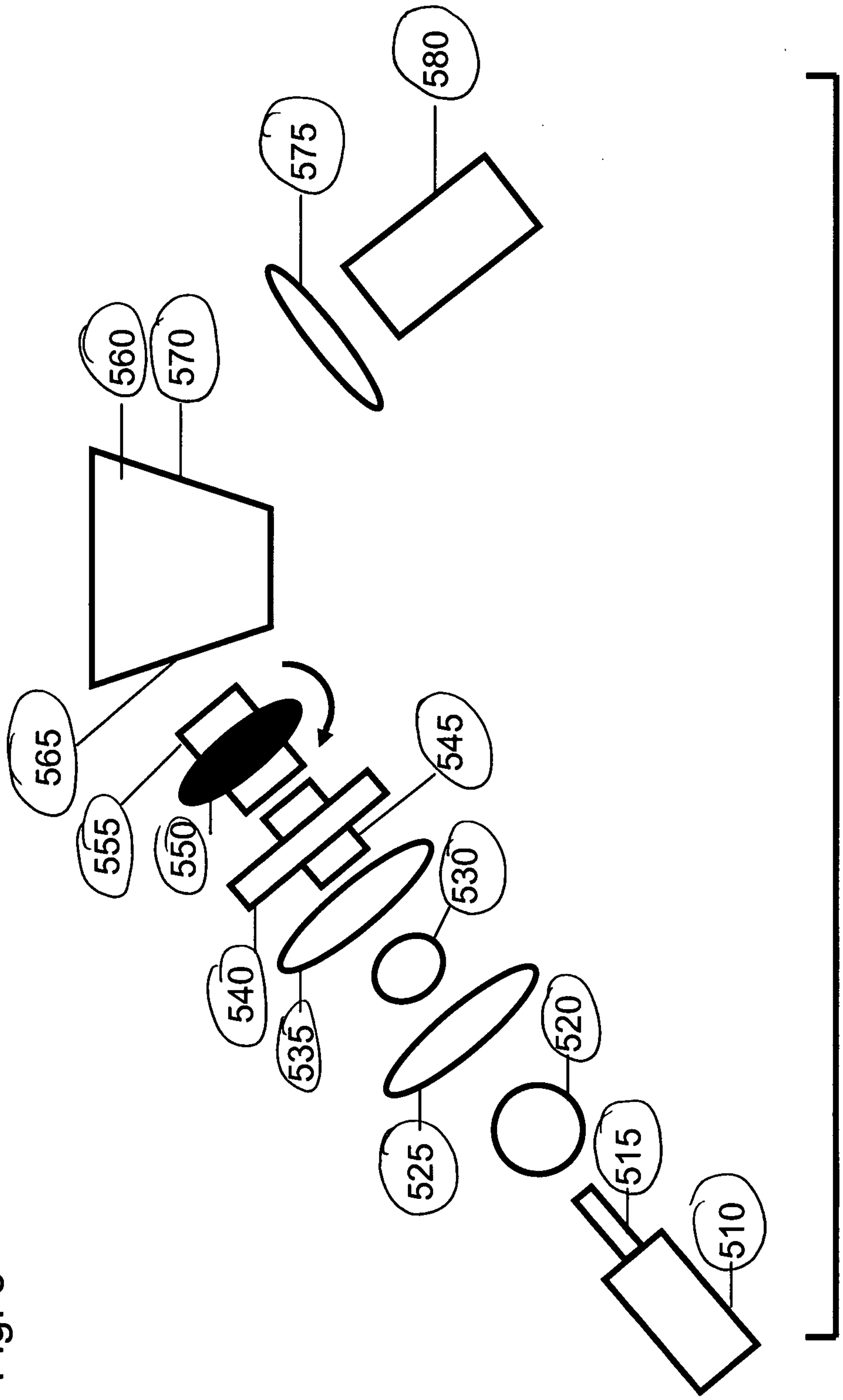

Fig. 5

EXHIBIT
A

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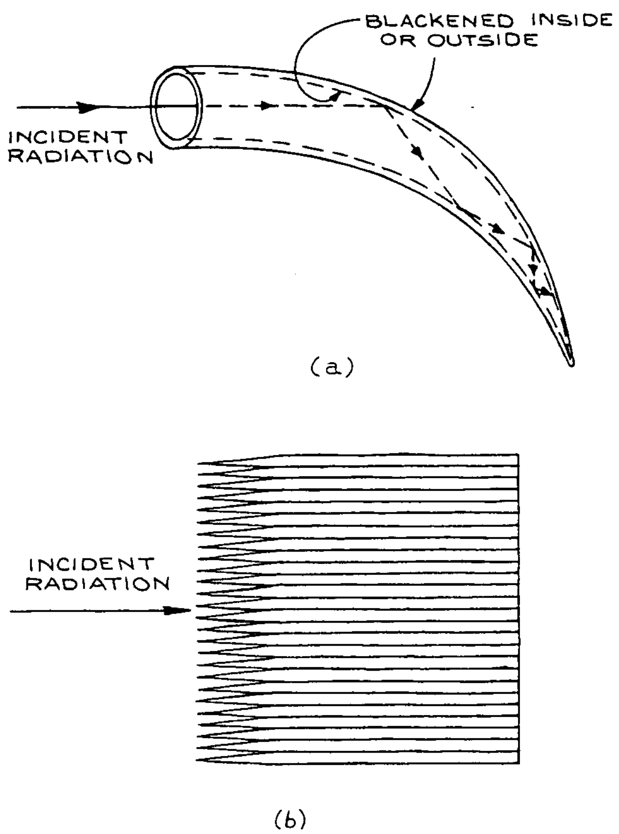


Figure 4.48 Light traps: (*a*) Wood's horn; (*b*) stacked razor blades.

reflections at an absorbing surface made in the form of a curved cone (usually made of glass); and a stack of razor blades, which absorb incident light very efficiently. Light traps are available commercially from Klinger.

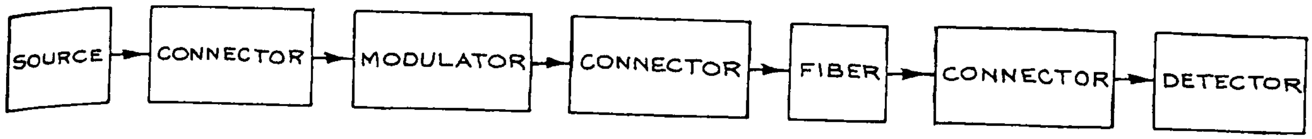
4.3.8 Fiber Optics

As is well known, the use of optical fibers has become widespread in the telecommunications field. Consequently, there are numerous suppliers of the various components and subsystems involved.[15] However, the use of optical fibers in scientific research can be a very valuable technique, and one that is not particularly complicated. For example, in experiments where r.f. interference, pickup, and ground loops are a problem, an experimental signal can be used to modulate a small light-emitting diode or laser. The modulated optical signal is then passed along an optical fiber to the observation location, where the original electrical signal can be recovered with a photodiode. Complete analog transmission systems of this kind are available from Meret, Honeywell, Microwave Semiconductor, Litton (Poly-Scientific), Math Associates, and Laser Diode. A schematic diagram of the various components of such a system is shown in Figure 4.49(*a*). The source may be supplied fabricated directly onto a fiber. The modulator is frequently unnecessary, as the source itself can be directly amplitude-modulated. The detector may also be supplied fabricated directly onto the end of the fiber. A few specific points are worthy of note for the experimentalist who may wish to utilize this technology.

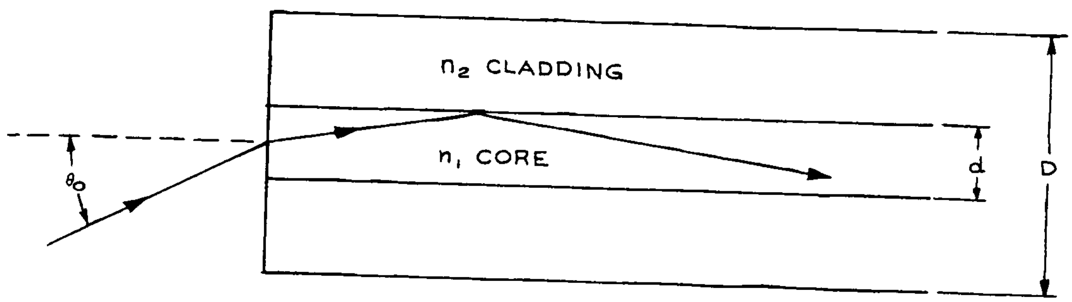
For certain laboratory applications the construction of a fiber system without any connectors is straightforward. Light from the source is focused into the end of the fiber with a microscope objective. Light emerging from the other end of the fiber is focused onto the detector in a similar way. A convenient range of microscope objectives for this purpose is available from Newport, who also supply a wide range of components for holding and positioning fibers. The choice of lens focal length and placement is governed by the *numerical aperture* (N.A.) of the fiber. The meaning of this parameter can be understood with reference to Figure 4.49(*b*), which shows a meridional section through a so-called *step-index* fiber. In this composite fiber the cylindrical core has refractive index n_1, and the surrounding cladding has index n_2, where for total internal reflection of rays to occur in the core, $n_1 > n_2$. Light entering the fiber at angles $\leqslant \theta_o$ will totally internally reflect inside the core. The N.A. is

$$\sin\theta_o = \frac{\sqrt{n_1^2 - n_2^2}}{n_1}.$$

Commercially available fibers typically have a smoothly varying radial index profile, but the N.A. is still the appropriate parameter for determining the acceptance



(a)



(b)

Figure 4.49 (*a*) Fundamental components of a fiber-optic data link. (*b*) Meridional section through a step-index optical fiber. The core refractive index is n_1; the cladding refractive index is n_2. The core and cladding diameters are d and D, respectively. A ray entering the fiber will be totally internally reflected provided its angle of incidence is less than θ_o, where $\sin\theta_o = \text{N.A.}$

angle. Two specific types of fiber are in most common use: single-mode and multimode. Single-mode fibers typically have core diameters on the order of 10 μm and cladding diameters of 125 μm. They require very precise connectors and are only needed in specialized experiments where the ability of the fiber to support only a single propagating mode is important. Multimode fibers have larger core diameters, from 50 μm to above 1 mm, and cladding diameters somewhat larger than their respective core diameters. These fibers are easy to use: the larger sizes are frequently used to channel light for illumination into positions that are difficult to access, or to collect light from one location and channel it to a detector somewhere else. Large fibers that are suitable for these purposes are available from Edmund Scientific and Eotec.

Fibers can be cut to provide a flat end face with the aid of specialist cleaving tools of varying degrees of precision and complexity, available from suppliers such as Newport and York. In simple experimental setups an adequate cleaved flat face can be obtained in the following way: (i) Remove the outer plastic protective coating from the cladding in the region that is to be cut by immersing this part of the fiber in methylene chloride (the active ingredient in most proprietary paint and varnish strippers). (ii) Lightly scratch the cladding with a cleaving tool (slightly more precise than a conventional glass cutter). (iii) Fasten one half of the fiber to a flat surface with masking tape, and pull the other half of the fiber axially away, keeping the fiber flat on the surface. This procedure usually gives a flat enough face for use with a microscope objective. However, if fibers are to be cut and connectorized, they must be cut and polished according to the instructions supplied with the connector. For fuller details of optical fibers and systems the specialized literature should be consulted.

Snell's Law, Reflection, and Refraction

In order to follow the quickest path through a system, a ray changes direction as it travels from a medium of one refractive index to another medium that has a different refractive index.

Snell's Law, which can be stated as

$$n_A \mathrm{Sin} q_A = n_B \mathrm{Sin} q_B$$

predicts how the ray will change direction as it passes from one medium into another, or as it is reflected from the interface between two media. The angles in this equation are referenced to a surface normal, as is illustrated below.

In the following figure, a ray is incident on an interface between two dissimilar media. A plane that includes the incident ray and a line drawn normal to the surface is called the plane of incidence. This plane also contains the reflected and *refracted* rays. A refracted ray is transmitted into the second medium and travels in a different direction than the incident ray. The angle that the incident, reflected, and refracted rays make with the surface normal are called the angles of incidence, q_i, reflection, q_r, and refraction, q_t, respectively. The refractive index of medium 1 is n_1 and of medium 2 is n_2.

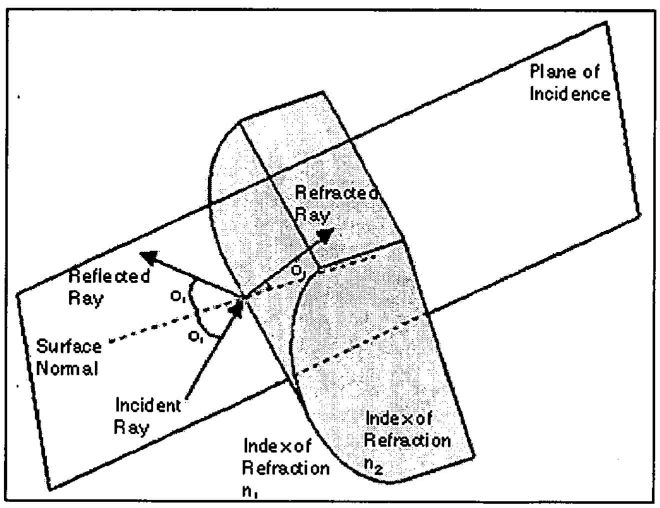


Illustration of Incident, Reflected, and Refracted Rays

In the case of a reflected ray, $n_A = n_B = n_2 = n_1$,

$$n_1 \mathrm{Sin} q_i = n_1 \mathrm{Sin} q_r,$$
which is the same as
$$\mathrm{Sin} q_i = \mathrm{Sin} q_r.$$

From this, it is easy to see that the angle of incidence and the angle of reflection are the same!

In the case of the transmitted, or refracted, ray,

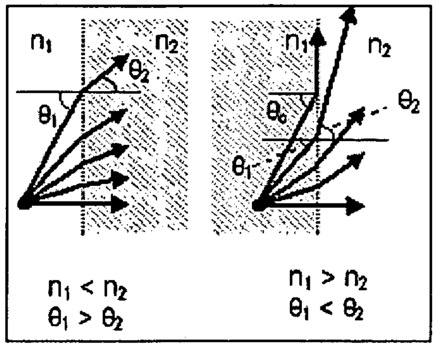
$$n_1 \mathrm{Sin} q_i = n_2 \mathrm{Sin} q_t.$$

If $n_1<n_2$, then the angle of refraction is always smaller than the angle of incidence. If $n_1>n_2$, then the angle of refraction is larger than the angle of incidence...when there is an angle of refraction! Imagine the angle of incidence getting larger and larger for the case of $n_1>n_2$. Eventually the refracted ray will make an angle of 90^o with the surface normal. If the angle of incidence is increased beyond that angle, then refraction does not occur! All of the light incident on the interface is reflected back into the incident medium! The smallest angle of incidence at which total internal reflection occurs is called the critical angle, q_c. Using Snell's law,

$$n_1 \text{Sin} q_i = n_2 \text{Sin}(90^o) = n_2.$$

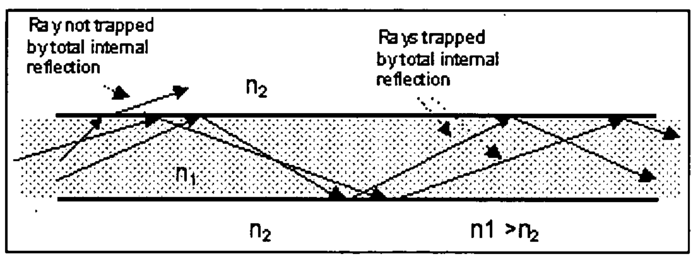
From this,

$$q_c = \text{Sin}^{-1}(n_2/n_1).$$



These Diagrams Illustrate Two Different Cases of Refraction. Total Internal Refraction is Depicted in the Sketch on the Right.

Many devices take advantage of the total internal reflection, including optical waveguides (like optical fiber). A waveguide is a length of transparent material that is surrounded by material that has a lower index of refraction. Rays that intersect the interface between the waveguide material and the surrounding material at angles equal to or larger than the critical angle are trapped in the waveguide and travel losslessly along it.

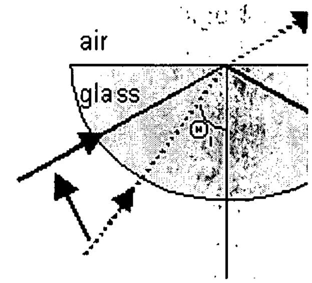


Rays Can be Trapped in a Waveguide Through Total Internal Reflection

Surface Plasmon Resonance

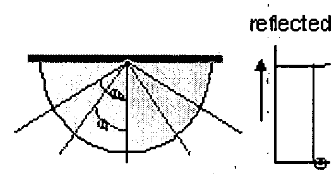
Surface Plasmon Resonance (SPR) is a physical process that can occur when plane-polarized light hits a metal film under total internal reflection conditions (1).

Total internal reflection



When a light beam hits a half circular prism, the light is bend towards the plane of interface, when it is passing form a denser medium to a less dense one. Changing the incidence angle (Θ) changes the out coming light until a critical angle is reached. At this point all the incoming light is reflected within the circular prism. This is called total internal reflection (TIR). Although no light is coming out of the prism in TIR, the electrical field of the photons extends about a quarter of a wave length beyond the reflecting surface.

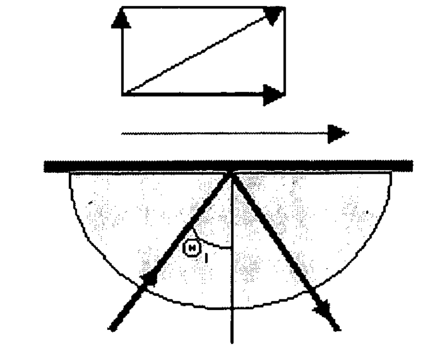
Surface plasmons

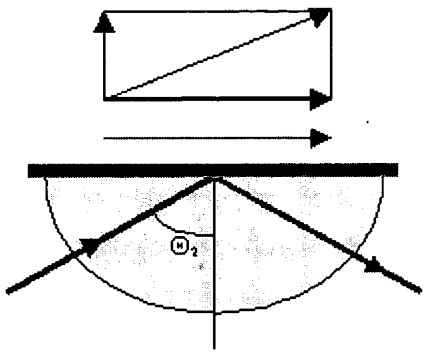


Now the prism is coated with a thin film of a noble metal on the reflection site. In most cases gold is used because it gives a SPR signal at convenient combinations of reflectance angle and wavelength. In addition, gold is chemical inert to solutions and solutes typically used in biochemical contexts (1). When the energy of the photon electrical field is just right it can interact with the free electron constellations in the gold surface. The incident light photons are absorbed and converted into surface plasmons. Photon and electron behavior can only be described when they have both wave and particle properties. In accordance with the quantum theory, a plasmon is the particle name of the electron density waves. Therefore, when in a TIR situation the quantum energy of the photons is right, the photons are converted to plasmons leaving a 'gap' in the reflected light intensity.

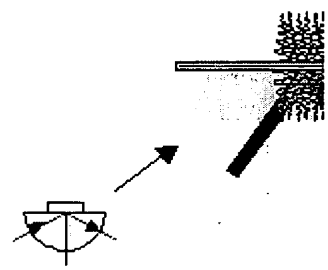
Momentum resonance

Like all conversions, the photon to plasmon transformation must conserve both momentum and energy in the process. Plasmons have a characteristic momentum defined by factors that include the nature of the conducting film and the properties of the medium on either side of the film. Resonance occurs when the momentum of incoming light is equal to the momentum of the plasmons (momentum resonance). The momentum of the photons and plasmons can be described by a vector function with both magnitude and direction. The relative magnitude of the components changes when the angle or wavelength of the incident light changes. However, plasmons are confined to the plane of the gold film, so for SPR it is only the vector component parallel to the surface that matters
Thus, the energy and the angle of incident light must be right to form surface plasmon resonance.





Evanescent wave



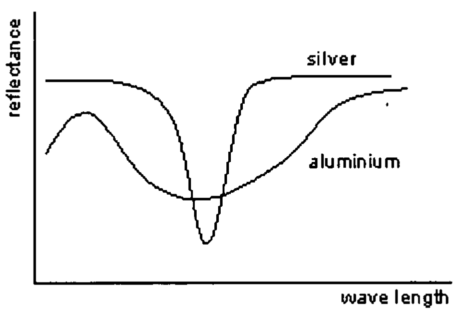
In TIR, the reflected photons create an electric field on the opposite site of the interface. The plasmons create a comparable field that extends into the medium on either side of the film. This field is called the evanescent wave because the amplitude of the wave decreases exponentially with increasing distance from the interface surface, decaying over a distance of about one light wavelength (2). The dept of the evanescent wave which is useful for measurements is within ~ 300 nm of the sensor surface (3). The wavelength of the evanescent field wave is the same as that of the incident light. The energy of the evanescent wave is dissipated by heat.
Equations, which describe how electric fields travel through a medium, include a term for the properties of the medium. For light, this term is the refractive index. The light is seen as refracted because the photons have a different velocity in different media.
In the same way, the velocity (and therefore the momentum) of the plasmons is changed when the composition of the medium changes. Because of the change in momentum, the angle of incident light at which the resonance occurs changes. This can be measured very precise (4). This type of SPR is known as resonant angle or angular SPR and is commonly used (5). On the other hand, at a fixed angle of incident light, the wavelength can be varied until resonance occurs (6). This is known as resonant wavelength SPR or spectral SPR and is not used widely.

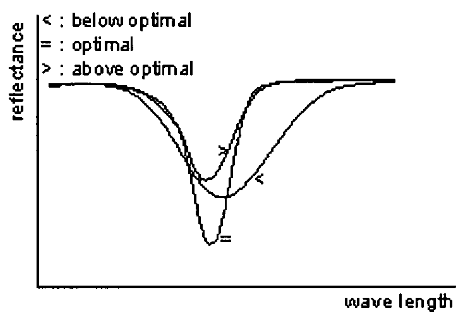
However, the best angular accuracy of the goniometer in angular SPR is 0.001°, which corresponds to an optical wavelength shift of 0.6 nm. A full wavelength spectrophotometer can simultaneously observe the wavelength from 400 - 800 nm and is more accurate than angle measurements.

SPR dependencies

The surface plasmon resonance angle mainly depends on the properties of the metal film, the wavelength of the incident light and the refractive index of the media on either side of the metal film (1). Because the refractive index is sensitive to temperature, it is important to perform the

measurements at defined temperatures. In some cases, this dependency can be exploited (7). The metal must have conduction band electrons capable of resonating with the incoming light at a suitable wavelength (8). Metals that satisfy to this condition are silver, gold, copper, aluminium, sodium and indium. In addition, the metal on the sensor surface must be free of oxides, sulphides and not react to other molecules on exposure to the atmosphere or liquid (8). Of the metals, indium is to expensive, sodium to reactive, copper and aluminum to broad in their SPR response and silver too susceptible to oxidation. This leaves gold as the most practical metal. Gold is very resistant to oxidation and other atmospheric contaminants but is compatible with a lot of chemical modification systems. The thickness of the gold should be ± 50 nm. The thickness of the metal layer is of great importance. Above an optimum the dip in reflective light becomes shallow, below the optimum the dip becomes broader (2). The light source should be monochromatic and p-polarized (polarized in the plane of the surface) to obtain a sharp dip. All the light which is not p-polarized will not contribute to the SPR and will increase the background intensity of the reflected light (2).





Since in experiments the metal film, the incident light and temperature are kept constant, the SPR signal is directly dependent on the change of the refractive index of the medium on the sensor side of the SPR surface.

Quantitative measurement

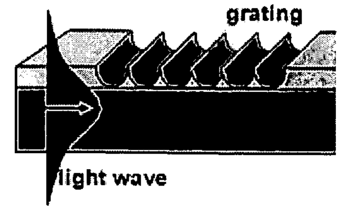
The binding of biomolecules results in the change of the refractive index on the sensor surface, which is measured as a change in resonance angle or resonance wavelength. Fortunately, the change in refractive index on the surface is linear to the amount of molecules bound (6). However this holds mainly for protein-protein interactions which have a refractive index increment (RII) of about 0.18-.019 ml/g (9). For other biomolecules, some calibration may be necessary. Most of the SPR-machines convert the actual measured values (angle or wave length) into an arbitrary one, which is easy to display and interpret. The BIACORE machine for instance uses the Resonance Unit (RU) which is converted from the actual angle shift in reflected light. Knowledge of the RII is important for many qualitative and comparative applications of SPR, especially with small molecules. In the process of screening combinatorial libraries, many small molecules are screened with a single concentration. For an accurate affinity ranking and correct stoichiometric measurements SPR response must be normalized for each compound (9). Fortunately the RII is not that important to get meaningful results in simple protein-protein interactions in which the kinetic constants are determined.

SPR configurations

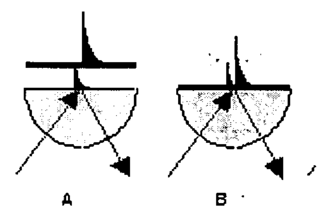
There are three general configurations of SPR devices that are capable to

generate and measure surface plasmon resonance (8).

- grating coupled systems
- optical waveguide systems
- prism coupled attenuated total reflection systems



For the grating coupled systems, the sinusoidal grating is the optimal grating. The period (top-to-top) and amplitude (top-to-trough) of the grating will determine the wavelength of resonance.
The optical waveguide systems have some attractive features like the simple way to control the optical path, small size and ruggedness. By varying the angle of incidence of the light, a light wave is guided by the wave guide. On entering the region with a grating (2400 lines/mm) and a thin metal overlay, it evanescently penetrates through the metal layer. At the end of the wave guide the outcoming light is detected by photodiodes. An algorithm is used to model the adsorbed material linearly to surface concentrations.



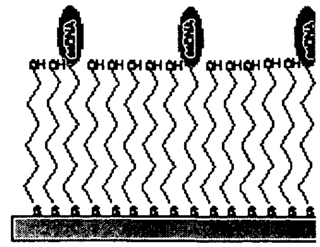
The prism based system of SPR can be applied in different configurations. In the Otto arrangement (10),(11) there is a distance between the metal and the TIR surface (A). The space is filled with a lower refractive index medium. This configuration is useful in the study of SPR in solid phase media. However since the distance between metal and TIR surface reduces the SPR efficiency it is less useful for applications with solutions (2). In the Kretchman configuration (12), the metal layer is directly on top of the TIR surface enabling a more efficient plasmon generation (B). A third configuration looks like the Otto arrangement but uses a special layer to enhance TIR (C). The coupling of the TIR light to plasmons is done by the resonant mirror (RM) principle (13). On a prism in which the light is in TIR a small layer of silica (~ 1 mm) is deposited. On top of the silica, there is a titania layer. The silica layer is thin enough to allow the evanescent field generated by in the prism to couple into the high refractive index titania. This so called frustrated total internal reflection (FTIR) allows the titania layer to function as an optical waveguide. Repeated total internal reflection of the guided mode within the wave guiding titania layer results in the production of an evanescent field at the titania-adlayer interface. The exact angle of incident light at which the resonance between the wave guided mode and the evanescently coupled light occurs is directly dependent upon the refractive index of the surface adlayer. Unlike the SPR device however, there is virtually no loss of the reflected light intensity associated with the resonance condition. Rather, resonance is accompanied via a 2? change in phase of the reflected light, which is recorded interferometically (13).

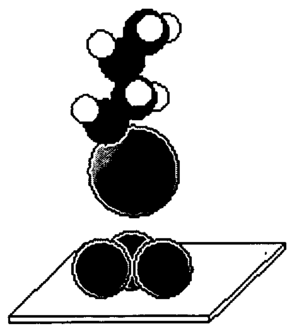
Sensor surface

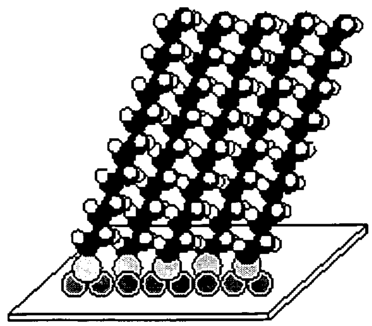
The actual sensor chip surface depends on the manufacturer and application to be used. Generally, a glass surface is coated with an inert metal (gold). On the metal, a self-assembled monolayer (SAM) is deposited. This can be ?-hydroxyalkanethiol (1) providing a linker layer to the metal surface and the next layer. On the SAM a matrix of non-crosslinked carboxymethylated dextran is bound which provides a hydrophilic layer. The dextran is a linear chain of glucose units and exhibits a very low non-specific adsorption of biomolecules. Each glucose unit is modified with one carboxy group (1). In most cases, the dextran hydrogel is the starting point to covalently bind a ligand to the sensor surface by amine-, thiol- or aldehyde chemistry.

A thiol compound and a gold surface is one of the well established

combinations of making a SAM. The n-alkanethiols ((HS-CH2)n-CH3, n > 10) is the most frequently used compound in producing SAM surfaces. The sulfur head group generally binds as a thiolate at the three fold hollow site at the AU (111) crystal lattice. A slight mismatch between the pinning distance and the van de Waals diameter of the alkyl chain, forces the molecules to assemble in a slightly tilted configuration in order to optimize the lateral interactions (2).







The SAM is easily made by dipping the gold surface in the alkanethiol solution. By using mixtures of modified alkanethiols several different SAM surfaces are easily made (14).

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